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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/029,479	10/21/98	LAVI S	2290.00061(T

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EXAMINER	
WOITACH,J	
ART UNIT	**PAPER NUMBER**
1632	16

DATE MAILED: 10/01/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

Office Action Summary	Application No. 09/029,479	Applicant(s) LAVI, SARA	
	Examiner Joseph Woitach	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-50,52-65 and 67* is/are pending in the application.

4a) Of the above claim(s) *45-48,53-64 and 67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49,50 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 October 1998* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application is a 371 national stage filing of PCT/IB96/01021, filed August 30, 1996 which claims benefit to provisional application 60/003,114, filed September 1, 1995.

Applicants amendment filed July 9, 2001, paper number 15, has been received and entered. Claims 51 and 66 have been canceled. Claims 49, 50 and 65 have been amended. Claims 45-50, 52-65 and 67 are pending. Claims 45-48, 53-64 and 67 are withdrawn from consideration as being directed to a non-elected invention. Claims 49, 50, and 65 are currently under examination.

Claim Objections

Claim 49 objected to because it depends on non-elected claim 45 is withdrawn. Claim 49 has been rewritten to be an independent claim obviating the basis of the rejection.

Claim 65 is objected to because it does not clearly reflect the elected invention of 'protein phosphatase 2C alpha'. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49, 50 and 65 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue that the specification teaches that expression of PP2Ca is decreased in many types of cancer, in particular PCR demonstrates that the level of PP2Cα in colorectal samples is decreased relative to surround normal tissue (Applicants amendment top of page 4 pointing to Example 5 in the specification). Applicants argue that one of skill in the art would know the proper level of expression one must attain for treatment, and point to the specification for the numerous examples needed to affect a proper form of treatment. Further, Applicants point to the same portion of the specification and argue that one can use the guidance in the specification to design the appropriate vectors for use in the claimed methods. Finally, Applicants argue that at the time of the claimed invention the targeted expression of a vector was highly reproducible, pointing to Fukushige *et al.*, Gage *et al.*, Holt *et al.* and FDA approved antisense drug treatment for CMV infections in the eye. See Applicants amendment, pages 5-6. Applicants arguments have been fully considered but not found persuasive.

In review the PCR data of figure 8, Examiner agrees that the expression of PP2Ca is decreased in the tumor sample tested, however the specification teaches that samples from other tissues show no or a varying change of expression and location of the PP2Ca in the cells tested (Example 4). As pointed out in the previous office action, the art teaches that various types of cancer do not show changes in PP2Ca expression when tested (Kitamura *et al.*). Presently, the

instant claims encompass the treatment of any type of cancer, however it is clear from the specification and the art of record that PP2Ca does not play a role in many types of cancers and thus, the specification fails to provide the necessary guidance which would provide a nexus between the decreased expression seen in a colorectal tumor sample and treating any type of cancer by gene therapy protocols. In addition, Examiner agrees that the specification discusses in general terms vectors which can be used in the claimed invention, and the examples provide more detailed guidance on the use of AAV as a possible vector. Applicants argue that expression of PP2Ca can alter the transformed phenotype of a cell, however while a review of the data in example 7 suggests that PP2Ca may play a role in the modulation of the activity of DNA polymerase, the clear correlation of the data is the influence of AAV silencing elements. More importantly, the data suggests that it is possibly the integration of the AAV, not PP2Ca expression which is important for the transformed phenotype. Further, none of the examples demonstrate that expression of PP2Ca can modulate the transformed phenotype of any human cancer or cancer cell line derived from a human.

Further, it is noted that the experiments pointed to for support of an enabling disclosure are done *in vitro* with cell lines in culture. Though working examples are not required to provide an enabling disclosure, because of the unpredictability of gene therapy protocols recognized in the art (as reviewed by Verma and Anderson) detailed guidance to the specific types of cells to be targeted for gene expression and a means to target said cells, guidance to the required levels of expression of the inserted gene and a means to obtain and control said levels of expression are required. The instant specification provides a general review of many possible vectors, however

fails to provide a nexus between a proposed role of PP2Ca expression in transformed cells with the necessary guidance for the skilled artisan to alter said expression such that any treatment is achieved. In addition, the specification fails to provide the necessary guidance to target the vector constructs to the cancer cells in a subject. The references and FDA approved protocol cited in Applicants arguments are not persuasive because they do not remedy the need for the specific guidance required to practice the instant invention. For example, the FDA approved protocol is for the administration of antisense oligonucleotides, however the administration of antisense oligonucleotides reduces the expression of a gene where the instant invention requires the increased expression of PP2Ca. The protocols set forth in the cited references, like those taught in the instant specification, represent different approaches for gene therapy but do not provide the necessary detailed guidance required to practice the specific methods as instantly claimed.

Applicants have proposed the expression of PP2Ca for the treatment of cancer in a patient, however essentially all of the work required to ultimately develop therapeutic methods has been left for others. Altered expression of a polynucleotide encoding PP2Ca may be demonstrated to have a role in cancer, however at the time the claimed invention was made, the instant specification does not provide the necessary teaching to provide a nexus between the proposed methods in the instant application and the art recognized problems associated with gene therapy. As discussed above and the previous office action, there are several art recognized limitations and unpredictability issues regarding gene therapy, that include: vector to be used for gene expression, production of effective concentration of the candidate polypeptide, delivery of the gene to the appropriated target cell, sustained expression and production of the candidate

protein *in vivo*, and maintaining an effective level of the enzyme *in vivo*. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). The Applicants have not described nor provided examples of how the recited method of gene therapy differs from those presently found in the art, and in great part rely on the methods of gene delivery established by others, Applicants face the same shortcomings faced by others skilled in the art with regards to the specificity of cell targeting and the ability to regulate gene expression.

Thus, in view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed. Therefore, for the reasons above and of record, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49 and 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically;

Claim 49 is unclear and vague in the recitation of 'determining the type of cancer and the cancerous cells' because it is not clear what is being determined or for what reason. In addition, the claim is confusing in the recitation of 'introducing the phosphatase into the cancerous cells by a vector' because the method is drawn to a method of administering a protein phosphatase to

cells, and there is nothing in the claim that indicates how this is accomplished by administering a vector. There is no indication what the vector encodes or what promoters are present which controls the expression. Further, the claim only recites that the method is accomplished by a vector, there are no active steps for the introduction of the vector nor are there any indications how the vector would be targeted to a cancerous cell. Dependent claim 50 is included in this rejection because it fails to clarify the basis of the rejection.

Conclusion

No claim is allowed. Claims 49, 50 and 65 are free of the art of record because the art fails to teach a method of treating cancer in a mammal by gene therapy protocols in which e the protein phosphatase 2C alpha is expressed, however the claims are subject to other rejections.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608. The fax number for group 1600 is (703)308-4724.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Karen M. Hauda

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Joseph T. Woitach